The liver–brain axis in metabolic dysfunction-associated steatotic liver disease

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Metabolic dysfunction-associated steatotic liver disease (MASLD) affects around 30% of the global population. Studies suggest that MASLD is associated with compromised brain health and cognitive dysfunction, initiating a growing interest in exploring the liver–brain axis mechanistically within MASLD pathophysiology. With the prevalence of MASLD increasing at an alarming rate, leaving a large proportion of people potentially at risk, cognitive dysfunction in MASLD is a health challenge that requires careful consideration and awareness. This Review summarises the current literature on cognitive function in people with MASLD and discusses plausible causes for its impairment. It is likely that a multifaceted spectrum of factors works collectively to affect cognition in patients with MASLD. We describe the role of inflammation, vascular disease, and brain ageing and neurodegeneration as possible key players. This Review also highlights the need for future studies to identify the optimal test for diagnosing cognitive dysfunction in patients with MASLD, to examine the correlation between MASLD progression and the severity of cognitive dysfunction, and to evaluate whether new MASLD-targeted therapies also improve brain dysfunction.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) affects around 30% of the global population.[1] MASLD represents a spectrum of disease severity spanning from simple steatosis, steatohepatitis with or without fibrosis, to cirrhosis, with an increased risk of hepatocellular carcinoma The MASLD diagnosis is assigned to people with hepatic steatosis, at least one of five cardiometabolic risk factors (obesity, insulin resistance, hypertension, hypertriglyceridaemia, or hypercholesterolaemia), and an average daily alcohol intake of less than 20 g for women and less than 30 g for men. The prevailing nomenclature for this disease changed in 2023, from non-alcoholic fatty liver disease (NAFLD) to MASLD to include the risk factors in the definition and avoid stigmatising language.[2] This new name emphasises the integral role of metabolic dysfunction in the disease, aligning with the understanding of fatty liver disease as the hepatic manifestation of the metabolic syndrome. The term MASLD is used throughout this Review, including when describing studies that were conducted before the nomenclature change. Importantly, more than 99% of patients with NAFLD meet the MASLD definition and have similar clinical profiles and mortality rates.[3,4]

The presence of hepatic steatosis and steatohepatitis serve as independent risk factors for type 2 diabetes, cardiovascular disease, and other extrahepatic comorbidities; therefore, MASLD should be considered a multisystem disease.[5] Over the past 10 years, a growing interest has emerged in exploring the liver–brain axis in MASLD, primarily due to the recognition of cognitive dysfunction in this patient group. Some of the key mechanisms progressing MASLD pathophysiology are low-grade inflammation, dysregulated metabolism of lipids and free fatty acids, gut dysbiosis, and systemic and hepatic insulin resistance that also challenge brain health.[6]

This Review summarises current literature on the liver–brain axis in MASLD. We focus on the potentially predominant causes for cognitive dysfunction in patients with MASLD—namely, the presence of chronic systemic inflammation, changes in cerebrovascular perfusion, and brain ageing and incipient neurodegeneration. We also identify knowledge gaps within the field and potential areas of future research.

Cognitive dysfunction in MASLD versus hepatic encephalopathy

Hepatic encephalopathy is a well established neurological complication caused by liver failure, which, in the context of cirrhosis, affects 30–40% of patients during their course of disease.[7,8] Clinically manifested hepatic encephalopathy (grade I–IV) can be preceded by a subclinical state of brain dysfunction termed minimal hepatic encephalopathy (MHE). This condition is detectable only by psychometric tests and is characterised especially by psychomotor slowing and executive dysfunction. Problems with executive function manifest primarily as difficulties with sustaining attention and working memory.[7] Over the past decade, there has been suggestion that patients with MASLD can also have deficits in cognitive function—even in the early stages of the disease, when there is no evidence of cirrhosis or liver failure (figure 1).

The first studies evaluating brain health in patients with MASLD were conducted by Newton and colleagues,[9,10] in 2008 and 2010. Nearly half of the included patients with MASLD had fatigue and cognitive impairment, which was the same proportion found in patients with liver cirrhosis caused by primary biliary cholangitis. In 2013, the same group reported difficulties with activities of daily function and physical abilities in 157 (70%) of 224 patients with MASLD attending a liver clinic. By comparison, these difficulties were reported in 80 (75%) of 107 patients with alcohol-related liver disease. Importantly, 70 (65%) patients with alcohol-related liver disease had cirrhosis, versus only 18 (8%) patients with MASLD, indicating that functional impairment exists well before cirrhosis develops in patients with MASLD.[11]

Since these first investigations, further studies have evaluated cognitive perfomance using various tests in patients with MASLD. Both small cross-sectional and case–control studies[12–14] and large cohort studies[15,16] have evaluated cognitive health in patients with MASLD using dementia screening tools, the Mini-Mental State Examination (MMSE) test, and the Montreal Cognitive Assessment. Overall, these studies suggest that patients with MASLD might have a global reduction in cognitive function, and the impairment seems to be independent of other confounders in younger patients (age 50–60 years).[13,16] Over time, the number of tests and their level of detail have been upscaled to explore the nature of cognitive symptoms in patients with MASLD. Seo and colleagues[17] conducted a cross-sectional study in the USA of 4472 adults using a complex series of tests designed to assess psychomotor speed, visual attention, learning, recall, and concentration. Participants with MASLD had deficits in all examined tasks compared with participants without MASLD, but, after controlling for cardiovascular disease risk factors, only the associations with learning, recall, and concentration remained statistically significant. The results were similar even in those without advanced fibrosis, excluding those with potential MHE. In a US-based cohort study by Gerber and colleagues,[18] similar associations between MASLD and impairments in processing speed, verbal memory, and executive function were found. Again, MASLD was associated with a less favourable cardiometabolic profile; when cardiovascular risk factors were adjusted for, the association of MASLD with cognitive impairment disappeared. Therefore, whether liver disease plays a direct causative role in cognitive dysfunction in people with MASLD remains unclear. It is likely that a multifaceted spectrum of factors work together to collectively affect cognition. This suggestion was put forward by Weinstein and colleagues,[19] who found that patients with MASLD and type 2 diabetes generally showed worse cognitive performance than patients with either MASLD or type 2 diabetes alone. As metabolic dysfunction is now encompassed within the diagnostic criteria for MASLD, adjusting for cardiovascular disease confounders might be less clinically relevant.

Recent studies of cognitive dysfunction in patients with MASLD have used validated tests for detecting MHE. In a study by Wernberg and colleagues,[20] 180 people referred for bariatric surgery were examined for liver disease and cognitive impairment, of whom 141 (78%) had MASLD. Three psychometric tests validated for MHE diagnosis were used and found cognitive impairment (defined as two or more abnormal test results) to be present in 14 (8%) of 180 patients. When conducting a subgroup analysis in 63 randomly selected patients using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a higher proportion of patients (26 [41%]) had cognitive dysfunction (authors used the reported cutoff less than 79 to define mild cognitive impariment, where a total index score of 100 is the norm), with immediate memory most commonly affected, followed by delayed memory and visuospatial functions. These patients also had abnormal test results in at least one of the three psychometric tests, mostly in the Continous Reaction Time test that assesses executive function and inhibitory control. RBANS captures broader cognitive areas, suggesting that brain dysfunction in obesity may be multidomain. Cognitive impairment was not restricted to patients with MASLD; however, this study did not report how many of the individuals with cognitive impairment and those with cognitive dysfunction had MASLD. Similarly, Giménez-Garzó and colleagues[21] recruited 59 patients with MASLD and 53 healthy individuals to undergo a series of psychometric tests, in addition to the Psychometric Hepatic Encephalopathy Score (PHES; the gold-standard for diagnosing MHE). In total, seven (12%) of the 59 patients with MASLD had an abnormal PHES, whereas around a third showed impairment in specific tests for selective and sustained attention, concentration, and processing speed. Similarly, Parikh and colleagues[22] found eight (12%) of 69 patients with MASLD in their cross-sectional study to have decreased cognitive flexibility and psychomotor speed in the EncephalApp test, which is a remote tool for MHE detection. However, 28 (41%) patients reported subjective cognitive impairment, and further cognitive testing additively showed that 17 (24%) patients had deficits in attention and inhibitory control. Thus, the psychometric tests validated to detect MHE appear to miss some of the cognitive changes that can be present in people with MASLD.

The heterogeneity in the pathogenesis and presentation of both MHE and MASLD-associated brain dysfunction makes it difficult to compare the deficits of the two conditions. A single validated psychometric test might not even capture the broad spectrum of MHE, as different cognitive domains can be affected in different patients. However, the findings of the aforementioned studies could imply that the presentations of cognitive impairment in patients with MASLD differ from (or only share some similarities with) those of MHE in patients with liver cirrhosis. This difference might be due to the

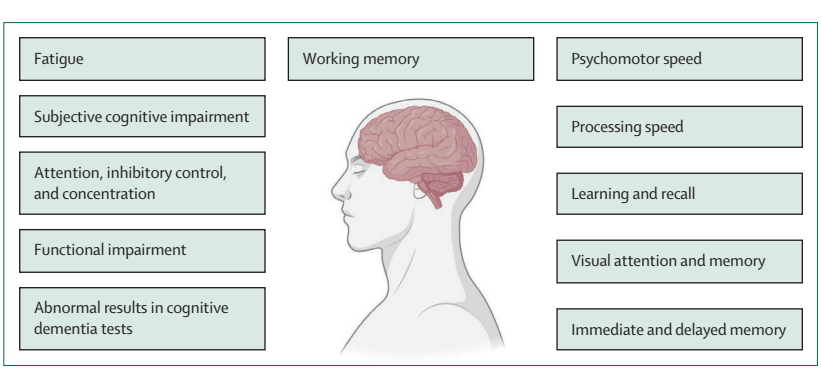

Figure 1: **Cognitive functions that might be affected in patients with MASLD**
MASLD=metabolic dysfunction-associated steatotic liver disease.

multiple possible contributors to brain dysfunction in patients with MASLD. Some of these contributors are similar to those involved in hepatic encephalopathy, such as systemic inflammation, gut dysbiosis, and metabolic liver dysfunction, which could lead to similar results in psychometric testing as seen in MHE. Other contributors, such as cardiovascular disease, insulin resistance, and obstructive sleep apnoea, are not associated with cirrhosis in general and might, therefore, affect distinct cognitive domains in people with MASLD. As such, using a broader neuropsychological battery of tests to assess cognitive deficits in patients with MASLD, instead of solely applying tests validated for MHE diagnosis, is essential. At present, further studies are needed to unveil the similarities and differences between MHE and brain dysfunction in patients with MASLD regarding both pathophysiology and presentation. For now, the term MHE should, therefore, be preserved for patients with liver cirrhosis.

Inflammation is believed to be a precipitator of hepatic encephalopathy, which has led to the hypothesis that patients with steatohepatitis have a higher risk of cognitive dysfunction than patients with simple hepatic steatosis. In the studies by Wernberg and colleagues[20] and Giménez-Garzó and colleagues,[21] all or most patients with MASLD had a liver biopsy, allowing for stratification of patients according to disease severity. However, neither the presence nor the grade of cognitive impairment differed between patients with steatosis versus patients with steatohepatitis in either study. This finding contrasts with those from a study by Miao and colleagues,[23] which found associations between the grade of steatosis, as well as the presence of hepatocellular ballooning, with impaired memory, even after controlling for confounders. However, most studies[12,13,15–19] examining cognitive function in people with MASLD diagnosed MASLD with imaging tools or non-invasive markers, and not liver biopsy, and so there are sparse data regarding the influence of different histological disease stages on cognition. Future studies in larger cohorts of patients with liver biopsy are needed to address this shortcoming.

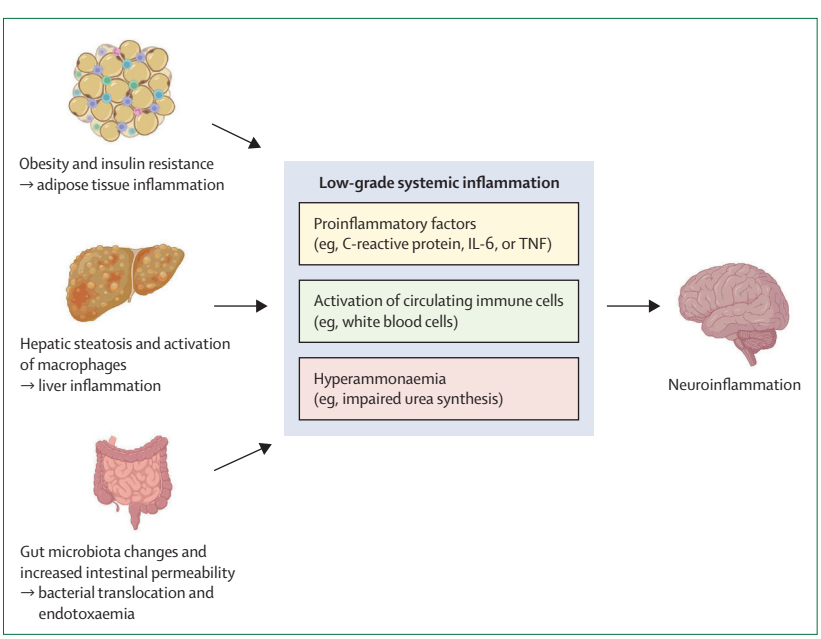

Figure 2: **The effect of inflammation on the liver–brain axis in MASLD**
MASLD=metabolic dysfunction-associated steatotic liver disease.

MASLD and inflammation

Patients with MASLD exhibit varying degrees of chronic systemic inflammation, which is regarded as an important mediator of extrahepatic complications in MASLD, including brain dysfunction (figure 2).[5] In the metabolic syndrome, obesity and peripheral insulin resistance stimulate adipose tissue inflammation, releasing adipokines and proinflammatory cytokines into the systemic circulation. The development of hepatic steatosis induces recruitment and activation of liver macrophages, contributing to the additional secretion of cytokines and chemokines into the bloodstream.[24] Alterations in the gut microbiota and increased intestinal permeability in patients with MASLD might facilitate increased activation of the innate immune system through bacterial translocation and endotoxaemia.[25] These processes serve to highlight that MASLD is a multisystem disease, with various organs communicating through persistent local and systemic low-grade inflammation. Accordingly, MASLD is independently associated with increased concentrations of circulating proinflammatory factors.[26] A direct link between hepatic injury and systemic inflammation is further substantiated by studies showing that lean patients with MASLD (without overweight or obesity) have similar plasma concentrations of proinflammatory cytokines to patients with MASLD and obesity.[27]

Although the effects of chronic systemic inflammation on brain dysfunction in patients with MASLD remain unclear, systemic inflammation constitutes a well accepted and important pathogenic factor for hepatic encephalopathy in patients with cirrhosis. In this situation, proinflammatory cytokines generally correlate with psychometric performance[28] and hepatic encephalopathy severity.[29] Emerging evidence indicates a similar relationship between inflammation and cognitive dysfunction in patients with MASLD. One cross-sectional study showed that poor performance (cognitive impairment) in the MMSE test in patients with MASLD was associated with the degree of systemic inflammation, as measured by increased white blood cell count and C-reactive protein.[30] Another small clinical study found that mild cognitive impairment (measured with various pschometric tests) in patients with MASLD was associated with a distinct immune phenotype characterised by increased activation of T-helper-17 lymphocytes and an overall increased plasma concentration of proinflammatory and anti-inflammatory

cytokines.[31] However, the effect of systemic inflammation on brain function in general remains to be fully understood. The prevailing theory is that systemic inflammation might extend to the brain and induce neuroinflammation,[32,33] an effect observed in animal models of hepatic encephalopathy.[34,35] However, evidence of neuroinflammation in patients with hepatic encephalopathy is scarce and results are conflicting.[36,37] Neuroinflammation is a complex process involving the activation of microglia and astrocytes within the CNS, stimulating further production of proinflammatory immune mediators. Chronic neuroinflammation is considered a key factor in the pathogenesis of various neurodegenerative disorders as it can directly interfere with brain function through altered neurotransmission, impaired neuronal plasticity, and perpetuating neuronal damage.[38] Interestingly, neuroinflammation has been observed in various brain regions of MASLD animal models.[39,40] A 2023 study by Kjærgaard and colleagues[41] found that rats with diet-induced MASLD developed hepatic and systemic inflammation, as well as increased microglia activation, diminished synaptic density in the prefrontal cortex, and an elevated concentration of the chemokine CXCL1 in the cerebrospinal fluid.[41] MASLD animals also exhibited impaired memory and depression-like behaviour. Neurobiological investigations in patients with MASLD are scarce. However, description of post-mortem samples have shown that people with metabolic dysfunction-associated steatohepatitis (MASH) have an increased activation of microglia and astrocytes, loss of granular and Purkinje neurons, and $CD4^+$ T-cell infiltration in the cerebellum.[42]

Notably, evidence from the field of hepatic encephalopathy has shown that systemic inflammation acts in synergy with hyperammonaemia to induce brain dysfunction.[43] Ammonia has neurotoxic effects and constitutes a well documented part of the pathogenesis of hepatic encephalopathy.[44,45] Systemic ammonia is eliminated through urea synthesis, a process that occurs exclusively in the liver.[46] The current definition of hepatic encephalopathy is brain dysfunction caused by liver insufficiency or portosystemic shunting,[7] which are the key factors driving hyperammonaemia. In MASLD-associated brain dysfunction, however, there is minimal deficit in liver synthetic function and an absence of clinically significant portal hypertension, despite which brain dysfunction is apparent even in early disease stages. A review by Jalan and Rose[47] suggests redefining hepatic encephalopathy to only include patients with brain dysfunction caused by liver cirrhosis or acute liver failure and liver disease-related hyperammonaemia. It has been previously shown that experimental and clinical MASLD leads to reduced capacity for urea synthesis at early stages of disease before cirrhosis development, resulting in decreased ammonia elimination and potentially hyperammonaemia.[48–52] In addition, researchers have hypothesised that hyperammonaemia could be further promoted in patients with MASLD by altered gut microbiota and intestinal permeability causing increased ammonia production by the enterobacteria and increased ammonia uptake to the systemic circulation.[53,54] Further research is needed to clarify the role of ammonia in pre-cirrhotic MASLD-associated brain dysfunction and to compare what is known with regards to the pathophysiology of hepatic encephalopathy in patients with cirrhosis. One small study showed that impaired psychometric performance assessed by PHES was observed in patients with MASH who had both hyperammonaemia and increased plasma IL-6, but not in patients with hyperammonaemia or increased plasma IL-6 alone.[55] Systemic inflammation during the metabolic syndrome is believed to cause disruptions in the blood–brain barrier, making it more permeable to circulating substances[56,57] such as ammonia; this theory remains to be tested in the context of MASLD.

Overt and subclinical cerebrovascular disease in MASLD

Overt or subclinical cerebrovascular disease is not an established part of the pathogenesis of hepatic encephalopathy,[58] but could be a leading candidate for driving brain dysfunction in MASLD. The presence of MASLD is closely associated with cardiovascular disease, as both conditions share common metabolic risk factors, such as obesity, type 2 diabetes, hypertension, and dyslipidaemia. One meta-analysis of 16 observational studies showed that the risk of fatal or non-fatal cardiovascular events was higher in patients with MASLD than in patients without MASLD (odds ratio [OR] 1·64, 95% CI 1·26–2·13).[59] The increased risk of cardiovascular events likely stems from an interplay between conditions that additively enhance the risk (figure 3). In addition to the well known cardiometabolic risk factors associated with the metabolic syndrome (obesity, insulin resistance, hypertension, hypertriglyceridaemia, and hypercholesterolaemia), pathophysiological changes caused by the liver disease itself in patients with MASLD might also directly contribute to the risk to cardiovascular and cerebrovascular health. The liver disease generates systemic inflammation, oxidative stress, hypofibrinolysis, hypercoagulation, dyslipidaemia, and insulin resistance, which are all stimulators of atherosclerosis and atherothrombosis.[60] MASLD has been independently associated with increased internal carotid intima–media thickness, endothelial dysfunction, and arterial stiffness, which places patients at risk of developing subclinical cerebrovascular disease and stroke.[61] Studies show that patients with MASLD have reduced grey matter cerebral blood flow[62] and reduced cerebral perfusion.[63] Reduced cerebral blood flow and perfusion might result in cerebral white matter lesions, which has been shown in patients with MASH and F2–F4 fibrosis.[64] The presence of white matter lesions seem to increase with MASLD severity, metabolic dysfunction, and fibrosis stage.[64]

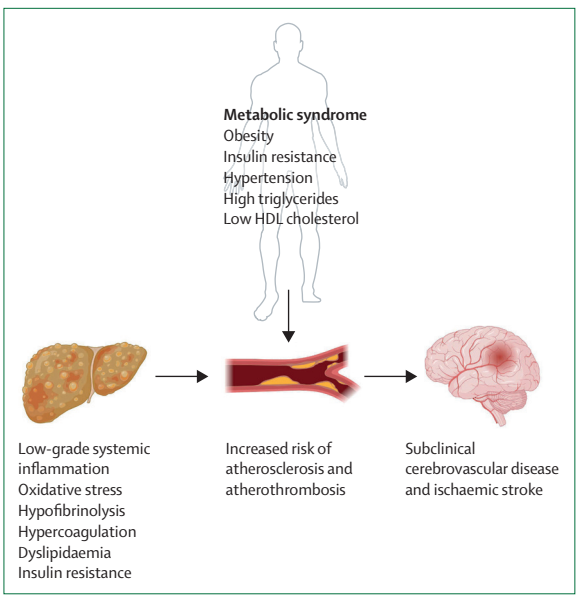

Figure 3: **The relationship between the liver and cerebrovascular disease in patients with MASLD**
MASLD=metabolic dysfunction-associated steatotic liver disease.

Subcortical infarctions are associated with mild cognitive impairment, dementia, and increased risk of stroke.[65] In 2022 and 2023, three different meta-analyses, covering studies from 2005 to 2021, were conducted to evaluate the risk of cardiovascular and cerebrovascular disease in patients with MASLD diagnosed by ultrasound, CT, ICD codes, Fatty Liver Index, or liver biopsy.[66–68] The reported ORs for ischaemic stroke were 1·41 (95% CI 1·29–1·55),[66] 1·68 (95% CI 1·22–2·30),[67] and 2·05 (95% CI 1·05–3·98),[68] suggesting a significantly higher risk of ischaemic stroke for this patient group than for patients without liver disease. Patients with MASLD did not have an increased risk of haemorrhagic stroke, most likely due to the different pathogenesis.[68] Following these meta-analyses, large population-based studies were conducted using data from more than 300 000 individuals derived from the UK Biobank[69] and data from nearly 10 million individuals derived from the Korean National Health Insurance Service.[70] The reported hazard ratios for ischaemic stroke in each study were 1·35 (95% CI 1·26–1·44)[69] and 1·33 (1·32–1·35),[70] respectively, compared to individuals without MASLD.

Most existing studies use imaging or non-invasive tools to define MASLD, and primarily focus on hepatic steatosis. The severity of hepatic steatosis seems to increase the risk of ischaemic stroke.[68] In addition, Simon and colleagues[71] evaluated major adverse cardiovascular events in Swedish patients with biopsy-confirmed MASLD and no underlying cardiovascular disease, matching them with population controls and following them up for a median of 13·6 years. Patients with MASLD had a higher incidence of major adverse cardiovascular events (including stroke) than controls, with rates progressively increasing with worsening histological severity at baseline, even after adjusting for confounders such as cardiometabolic risk factors and alcohol use. Non-invasive measurements of liver fibrosis in patients with MASLD similarly showed that the presence and severity of advanced fibrosis increased the risk of stroke.[72]

Additional studies suggest that coexistence of metabolic dysfunction with hepatic steatosis is decisive for the risk of stroke. Data from four European, population-based primary care databases showed that patients with MASLD or MASH had an increased risk of stroke, which was downsized gradually with progressive adjustment for cardiometabolic risk factors.[73] Chen and colleagues[69] found an increased risk of ischaemic stroke for patients in the UK Biobank who fulfilled the new MASLD criteria, but not for patients with hepatic steatosis who were overweight without metabolic dysfunction. Notably, the increased risk of ischaemic stroke remained for patients with lean MASLD (hepatic steatosis and metabolic dysfunction). This finding aligns with a previous meta-analysis showing a similar risk of major adverse cardiovascular and cerebrovascular events in both people with lean and non-lean MASLD.[67] Although patients with lean MASLD have a better metabolic profile in general, their risk of disease progression is equal to that of patients with non-lean MASLD, which might explain the similar risk estimates.[74]

Brain ageing and neurodegenerative disease in MASLD

The relevance of MASLD to brain ageing and neurodegenerative disease pathology is largely related to the cardiometabolic risk factors that are part of the MASLD definition. Individually and together, they have the potential to contribute to brain ageing and, some have posited, the pathogenetic pathways of Parkinson's disease and Alzheimer's disease, not only through increased rate of cardiovascular disease, but also through mitochondrial dysfunction and neuroinflammation.[75] Therefore, MASLD could accelerate the pathology of neurodegenerative diseases through shared common risk factors and pathogenetic pathways. By contrast, hepatic encephalopathy in patients with liver cirrhosis has traditionally been considered a reversible metabolic disorder. However, some studies suggest that repeated or extreme episodes of hepatic encephalopathy can lead to long-term changes, with persistent cognitive impairment and neuronal loss not being corrected by liver transplantation.[58,76–78] As 1-year mortality among patients with hepatic encephalopathy is high,[79] the timeframe in which hepatic encephalopathy occurs and reoccurs is likely too short for neurodegenerative diseases to develop.

Studies examining the connection between MASLD and brain ageing are scarce. A 2024 study pooled data from three population-based cohorts and analysed brain MRI measures in people with MASLD.[80] It found MASLD to be

associated with reduced volumes of total brain and grey matter, even after adjusting for body fat, hypertension, and diabetes.[80] Another study showed that patients with hepatic steatosis overall had a decrease in cerebral brain volume corresponding to 4·2 years of brain ageing when compared with individuals without steatosis, with this difference being 7·3 years for those younger than 60 years.[81] Whether this suggested link between MASLD and brain ageing results in dementia is uncertain. In older patients, MASLD was found to be protective for incident dementia in one study (age 65 years or older),[82] whereas another study found MASLD to slightly increase the risk of dementia, especially in those with concurrent heart disease or stroke (age 85 years or younger).[83] Having MASLD in midlife (age 50–60 years) has been reported to be associated with plasma biomarkers of Alzheimer's disease, cerebral vascular pathology, and an increased risk of cognitive decline and dementia in later life,[84,85] suggesting that a midlife onset of MASLD might increase the risk of neurodegeneration. Accordingly, middle-aged patients with MASLD and liver fibrosis showed early signs of Alzheimer's disease pathology, with accumulation of tau and amyloid β plaques in the brain, independent of cardiometabolic risk factors.[86] A possible explanation for this link is that the liver might be important in the turnover of amyloid β and so its consequent, pathological accumulation in the CNS. Wild-type and amyloid precursor protein-mutated mice both developed reversible liver pathology, including inflammation, and reversible, Alzheimer's disease-like pathology in the brain following a high-fat or Western diet (to model MASLD), supporting a role for MASLD-like liver dysfunction in Alzheimer's disease.[87,88]

Pathogenetic pathways common to the most prevalent neurodegenerative diseases include protein accumulation, misfolding, and aggregation; mitochondrial dysfunction; and neuroinflammation.[89] The pathology of Alzheimer's disease includes accumulation of amyloid plaques and tau, whereas the pathology of Parkinson's disease includes accumulation of α-synuclein aggregates as Lewy bodies and Lewy neurites. These neurodegenerative diseases are both associated with mitochondrial dysfunction, which causes increased free radical generation and contributes to inflammatory-mediated damage. The pathophysiology of MASLD-associated brain dysfunction involving similar pathways is a possibility. Microglial activation is thought to have an important role in disease progression of both Alzheimer's disease and Parkinson's disease; however, this role might differ with time or pathology. For instance, microglial activation could be an early protective response to protein aggregation and synaptic dysfunction, but a contributor to neurodegeneration later in the disease. In patients carrying *GBA1* gene mutations that are associated with Parkinson's disease, increased microglial activity has been noted before the onset of any dopaminergic cell dysfunction or clinical features of Parkinson's disease, signifying inflammation as an early feature of pathology.[90] Another study found increased microglial activity to be associated with a high-risk stratification for dementia based on cognitive tests and genotype in newly diagnosed patients with Parkinson's disease.[91]

Some epidemiological studies have provided conflicting results for the association between MASLD and Parkinson's disease. There was a reduced risk for Parkinson's disease in men with hepatic steatosis but an increased risk for women in a South Korean, registry-based study.[92] A community-based study in Rotterdam, the Netherlands, found no association between Parkinson's disease and MASLD.[93] By contrast, the association of type 2 diabetes with Parkinson's disease has been supported by several epidemiological studies, with most reporting both an increased prevalence of type 2 diabetes in patients with Parkinson's disease and an increased risk of Parkinson's disease in patients with type 2 diabetes.[94] A Mendelian randomisation study found no evidence of reverse causality between type 1 diabetes and Parkinson's disease or Alzheimer's disease, supporting the hypothesis that it is the insulin resistance contributing to the risk of neurodegenerative disease in people with type 2 diabetes.[95] Li and colleagues[96] reported that untargeted serum metabolic profiling found statistically significant associations between type 2 diabetes and Parkinson's disease. The link between type 2 diabetes and Parkinson's disease has been exploited in the development of GLP-1 receptor agonists for slowing progression in Parkinson's disease: two phase 2 trials have shown that motor function deterioration can be prevented,[97,98] whereas a third phase 2 trial of extended-release exenatide showed no benefit in early untreated patients with Parkinson's disease.[99] A phase 3 study of once-weekly exenatide is expected to report results in late 2024 (NCT04232969). Additionally, semaglutide, another GLP-1 receptor agonist, is currently being tested as a treatment for early Alzheimer's disease in a phase 3 study (NCT04777396).

Progression of MASLD has been linked to a disruption of bile acid homoeostasis, with increasing serum concentrations of bile acids.[100] Dysregulated bile acid homoeostasis is also present in liver cirrhosis,[101] and increased concentrations of bile acids have been found in the cerebrospinal fluid of patients with hepatic encephalopathy.[102] Research into the role that bile acids have in CNS function is growing.[103] There is evidence for both direct and indirect physiological actions of bile acids on the CNS. For example, bile acids might cross the blood–brain barrier and interact with brain farnesoid X receptors and the G-protein-coupled bile acid receptor 1, or via central GLP-1 receptor agonist activation following release from the intestine. Bile acids can cause GLP-1 receptor agonist release from the intestines, which can then stimulate receptors in the brain.[104,105] Changes in the bile acid profile associated with MASLD (potentially related to dysbiosis) could contribute to the pathogenesis of particular

neurodegenerative diseases through, for instance, inducing alterations in lipid function and therefore enhancing protein aggregation. In patients with Parkinson's disease, lower concentrations of chenodeoxycholic acid, cholic acid, and ursodeoxycholic acid were significantly associated with mild cognitive impairment.[106] One study investigating bile acid profiles in people with Parkinson's disease post mortem found primary bile acid biosynthesis as the major biochemical pathway to be perturbed in the frontal lobe.[107] Although detailed studies of bile acid profiles in patients with Parkinson's disease are awaited, studies have discussed using bile acids in the treatment of Parkinson's disease.[108] A 2023 phase 2 clinical trial of ursodeoxycholic acid in patients with Parkinson's disease showed favourable safety, tolerance, and improved ATP production in the brain, per magnetic resonance spectroscopy.[109] Further studies are needed to clarify how increased bile acids in MASLD affect the risk of developing Parkinson's disease.

Other contributors to cognitive dysfunction in patients with MASLD

In this Review, we have focused on the major, most probable causes for cognitive dysfunction in patients with MASLD: chronic systemic inflammation, changes in cerebrovascular perfusion, brain ageing, and incipient neurodegeneration. However, as patients with MASLD often have many comorbidities, other potential contributors to cognitive dysfunction might coexist in each individual patient. For instance, MASLD is associated with an increased risk of depression and anxiety,[110–113] of which especially depression has been shown to affect executive function, learning, and memory.[114] Moreover, the altered gut microbiota observed in people with MASLD[115] might also contribute to cognitive changes. In patients with cirrhosis, a dysfunctional microbiome–gut–liver–brain axis constitutes an important pathophysiological link in hepatic encephalopathy,[116,117] and preclinical data suggest that this axis is also implicated in cognitive dysfunction observed in animal models with pre-cirrhotic MASLD.[118,119] Altered gut microbiota might also increase the endogenous production of alcohol in patients with MASH,[120] but whether the resulting blood alcohol concentrations are sufficient to affect brain function is unknown. Furthermore, MASLD is associated with obstructive sleep apnoea.[121,122] Obstructive sleep apnoea is characterised by repetitive complete or partial collapse of the upper airways during sleep, causing intermittent hypoxaemia and disrupted sleep,[123] potentially inducing daytime somnolence and cognitive impairment.[124] In the context of MASLD, one study showed that obstructive sleep apnoea in patients with MASLD was associated with reductions in the volumes of cortical and subcortical brain structures, as well as cognitive impairment.[125]

Search strategy and selection criteria

References for this Review were identified by searching PubMed for papers published in English between database inception and March 27, 2024, using the search terms "metabolic dysfunction-associated steatotic liver disease" OR "MASLD" OR "metabolic dysfunction-associated steatohepatitis" OR "MASH" OR "non-alcoholic fatty liver disease" OR "NAFLD" OR "non-alcoholic steatohepatitis" OR "NASH" AND "x" ("x" indicates terms relevant to subtopic; for example, "cognitive dysfunction" OR "cognitive impairment" OR "cognitive health" OR "cognition" or "brain ageing" OR "neurodegenerative disease"). We also considered the relevant citations in these papers. Articles were also identified through searches of the authors' own files. The final reference list was generated based on originality and relevance to the broad scope of this Review.

Knowledge gaps and future perspectives

The prevalence of MASLD is increasing at an alarming rate.[1] The fact that a large proportion of these patients might be at risk of cognitive dysfunction represents a substantial health challenge that requires careful consideration. MASLD is an independent risk factor for type 2 diabetes and cardiovascular disease, reinforcing the idea that MASLD is a multisystem disease. This notion calls for careful management to reduce the risk of both liver and extrahepatic disease progression, which share common pathophysiological mechansims such as inflammation and dyslipidaemia.

When diagnosing cognitive dysfunction, the current challenge remains in defining an optimal test to discern cognitive dysfunction in patients with MASLD, given that the psychometric battery of tests used in studies to date is largely validated for MHE, which is a different disease entity. Similarly, cognitive tests used to assess cognitive decline with ageing and dementia are equally likely to not reflect the specific disease mechanisms relevant to liver injury and metabolic risk factors. Further studies are also required to map how the progression of MASLD correlates with changing severity of cognitive dysfunction, which remains unclear from current data. Another gap in the literature is the need to define clear criteria for staging MASLD with non-invasive tools so researchers can better relate MASLD progression to the severity of extrahepatic disease (including brain dysfunction). Clear criteria will be important in future studies evaluating the risk of major cardiovascular events given discrepancies shown between imaging, elastography (MRI and vibration-controlled) and histology for staging MASLD.

As new targets for MASLD therapy emerge, understanding the mechanisms underpinning extrahepatic disease, and specifically brain dysfunction, will be important. There are likely common pathophysiological pathways that facilitate both MASLD progression and end-organ injury, as seen in the progression of other liver

diseases, such as chronic hepatitis C and alcohol-related liver disease. For example, can targeting liver steatosis and the trigger for inflammatory pathways within the liver also reduce levels of brain inflammation? Evaluating this question during the development of new agents (eg, thyroid hormone receptor agonists such as resmetirom, antisense inhibitors of DGAT2, and GLP-1 receptor agonists) will be fundamental to assess their effects on brain dysfunction. Furthermore, given previous data[49] suggesting the presence of urea cycle dysfunction in patients with MASLD, whether ammonia-lowering strategies will have merit in improving cognitive function in patients with MASLD remains to be established. Irrespective of BMI, patients with MASLD seem to have an increased risk of cerebrovascular disease, which might present with brain dysfunction. Given this risk, a holistic approach to care should be implemented to ensure appropriate management of metabolic profiles to reduce cerebrovascular risks and potential drivers of MASLD progression. The development of new treatments potentially also targeting the liver–brain axis provides hope for the considerable number of patients with MASLD whose quality of life is being negatively impacted by brain dysfunction.

Contributors

Conceptualisation, review, and editing: RPM and KLT. Data curation and writing of original draft: ACDM, KK, and AHVS. Visualisation: ACDM. All authors contributed significantly to this manuscript, and read and agreed to the submitted version of this manuscript.

Declaration of interests

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